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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	9

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/899,440	STEIN, CY	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-28* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's IDS filed December 17, 2002 has been considered.

2. Applicant's amendment of claims 1, 7, 9, 20, and 28, and cancellation of claim 8 has been noted and entered. Applicant's response filed December 17, 2002 has been considered. Rejections and/or objections not reiterated from the previous office action mailed August 27, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 15, 16, and 21-27 stand rejected, and claims 17-20 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of heparanase expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of heparanase expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, and is repeated for the reasons of record set forth in the Office action mailed August 27, 2002.

The above invention is drawn to methods of inhibiting the expression of heparanase in a cell which may be a cancer cell comprising contacting said cell with antisense compositions that inhibit the expression of heparanase. The claims of the above invention are also drawn to methods of treating a subject having a condition associated with heparanase, wherein said compositions are administered to animals such that expression of heparanase is inhibited, wherein said condition may be cancer, which may be characterized by tumor metastasis, or involves reduction of angiogenesis, and to compounds comprising a carrier that may be a membrane permeable cationic reagent, or are effective to inhibit expression in a cell, or can pass through a cell membrane, wherein the language of said compound claims encompasses *in vivo* activity. The specification teaches a method of using the claimed compositions to inhibit the expression of heparanase in T24 bladder carcinoma cell line. Claims 17-20 are newly included in this rejection, because of functional language in said claims directed to methods of using the presently claimed compounds in cells encompassing *in vivo* applicability.

Applicant argues that M.P.E.P. § 2164.03 requires only a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity for enablement. It is also argued that Applicant's disclosure describing that antisense oligos have inhibited the transcript *in vitro* indicates that it can traverse the physical barriers mentioned in Braasch et al., and can thus be taken up as required by Agrawal, and that the examiner has not explained why the oligos would need to be taken up with the same efficiency by different cell types in order to be active in those cells. Applicants point out that Agrawal teaches that antisense oligos can inhibit disease-associated proteins, that the specificity of such methods has been verified in animal models, and

that Tamm et al. teaches FDA approval of the therapeutic use of antisense oligos. Applicants argue that the problems of non-specific toxicity as delineated by Tamm et al. does not preclude activity or usefulness, that dosage issues can be resolved by routine experimentation. Applicants assert that the previous Office action did not cite reasons why the instantly claimed oligos would not have *in vivo* activity, and that the *in vitro* experimentation of the specification provides a reasonable correlation with the *in vivo* situation as exemplified in references provided by Applicant. Finally, Applicants perceive the enablement rejection of the previous Office action as requiring low toxicity, low immunogenicity, and a complete lack of harmful heparanase expression for patentability, and state that these are unreasonable demands upon Applicant.

Applicant's arguments have been fully considered but they are not persuasive. The five review articles cited in the previous Office action are considered to continue to demonstrate a high level of unpredictability in the development of therapeutic methods utilizing antisense oligos. Furthermore, as exemplified in the aforementioned references, the *in vitro* exemplification is not considered to be adequately representative of the dynamic *in vivo* environment such that one skilled in the art would not readily be able to use the instant antisense oligos for *in vivo* use and to further provide treatment without engaging in undue experimentation (see previous Office action for the precise reasons why). While it is noted that some occurrences of success using antisense oligos *in vivo* do exist, the references previously cited clearly indicate that such occurrences do not represent the state of the art as a whole. Further, success of one or even a few antisense studies is not generally representative of success as a whole for being able to design and deliver antisense oligos *in vivo* and further, for treatment.

In arguing that Applicant's antisense oligos of the disclosure are capable of inhibiting the transcript *in vitro,* which in turn indicates that said oligos can traverse the barriers mentioned in Braasch et al., and further, that these oligos can thus be taken up as required by Agrawal, it is noted that the previous Office action stated that Applicant was enabled for such *in vitro* use. Insofar as it is Applicant's position that this *in vitro* evidence provides enablement for the use of said oligos *in vivo,* it is pointed out that Applicant's use of an *in vitro* model system does not re-create the complex extracellular milieu comprising the myriad of plasma and cell surface proteins that such oligos are expected to encounter, or re-create the immune response discussed in the prior Office action, before ever reaching the target. For these reasons, Applicants' assertion that the instant oligos traverse cell membranes in a culture dish does not adequately correlate with the environment these oligos would encounter *in vivo*, and therefore does not suggest that the same will happen *in vivo*. As mentioned in the previous Office action and reiterated here, significant non-specific binding of oligonucleotides, and particularly the phosphorothioated versions contemplated presently, are known in the art to bind problematically to unintended targets, causing experimental artifacts that can't be predicted from results obtained *in vitro*. Applicants' specification does not provide any resolution to this art-recognized problem, in particular as it relates to targeting the instant gene and providing treatment by inhibiting it.

Applicants state that the examiner must provide reasons why the correlation between *in vitro* data on antisense compounds to *in vivo* effects is unpredictable. In response it is noted that the focus of these articles is the application of antisense-mediated inhibition *in vivo,* and further

that this goal so far has been unattainable in any predictable fashion. This theme underlies all the literature cited in the previous Office action. For example, in Branch et al. on page 49, far right column, line 25-30, the subject of unpredictability is broached; "With so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells." Gewirtz et al. indicate (at page 3162, center column, 2nd to last paragraph) that studies of a transfection agent GS2888 complexed with antisense oligos have been successful in cell culture, but studies in primary cell lines are needed, and adds that "while the application of GS2888 [a transfection agent] to cell culture experiments has been clearly demonstrated, its utility for therapeutic applications remains to be determined." Such language underscores the difficulties in moving from *in vitro* cell culture experiments to the *in vivo* whole animal. Agrawal et al. devotes the closing section on the unpredictabilities of *in vivo* efficacy, how moving from cell culture to the *in vivo* whole animal is an important hurdle where no reasonable degree of success can be assured. These passages all imply or explicitly state difficulty in attaining therapeutic success, and emphasize that such success has been elusive.

Regarding Applicants' assertion that the specificity of antisense methods has been verified in animal models, and that Tamm et al. teaches FDA approval for the therapeutic use of antisense oligos, it is reiterated that the intermittent occurrences of success using antisense oligos *in vivo* are considered to be outweighed by the failures and skepticism of researchers in the field. For example, and as set forth previously, Braasch et al. states that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable

technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2)," and "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death..." Branch confirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis." Branch states in the abstract that the promise of antisense drug design is considerable, "However, they are far more difficult to produce that was originally anticipated, and their ability to eliminate the function of a single gene has never been proven." When these references are viewed as a whole as required, it is apparent that Applicants arguments have wholly ignored the broad statements regarding the unpredictable state of the art of these authors, in favor of a piecemeal presentation of the infrequently noted successes.

For these reasons, the *in vitro* experimentation and prophetic guidance of the specification is not viewed as providing a reasonable correlation with the *in vivo* situation as exemplified in references above or, that the instantly claimed oligos would actually have *in vivo* activity. Furthermore, Applicants only assert that the problems of non-specific toxicity and dosage issues can be resolved by routine experimentation, but provide no evidence that these issues could ever be resolved routinely or without engaging in undue experimentation, particularly in view of the cited unpredictibility in the art as described above and in the prior Office action. It is apparent for these reasons that one of skill in the art in attempting to practice the steps as recited in the claims would do so with no reasonable degree of certainty that

treatment to any degree would be provided. Based on the lack of specific guidance in the disclosure as filed on how to deliver the instant antisense to the target in order to achieve some therapeutic effect in view of the known unpredictability in the art, the quantity of experimentation would thus require the de novo determination of a variety of factors needed to provide for the delivery and further treatment effects *in vivo*. As originally set forth, this is considered to require an undue amount of experimentation since the state of the art nor Applicant's disclosure provide any specific guidance for practicing the invention *in vivo* and or further for treatments as claimed.

Finally, the prior Office action does not require Applicants to provide formulations with low toxicity, low immunogenicity, and a complete lack of harmful heparanase expression for patentability. These issues were pointed out in an effort to point out the wide gap between the art-recognized problems of using nucleotide oligos in therapeutic treatments and the breadth of Applicant's claims, and also the quantity of experimentation required to enable these broad claims. Toxicity, immunogenicity, and targeting are all issues that pertain to Applicants claimed invention of providing therapeutic treatment; while these issues are not required to be fully resolved in order to be enabled, they are nevertheless real barriers towards the successful practice of such treatment methods, and remain unaddressed in any manner in Applicant's disclosure. In summary, Applicant's failure to disclose some facts or guidance leading one skilled in the art to be able, through reasonable experimentation, to provide any treatment other than by prophetic guidance makes it clear that the amount of experimentation required to attain successful

therapeutic treatments of the type claimed by Applicant that at least consider the art recognized issues of toxicity, immunogenicity, and targeting is prohibitively high.

5. Claims 1-6, 9-15, 17-20, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kussie et al. (Biochem. Biophys. Res. Comm. 1999. 261:183-187, Applicants IDS), in view of Pecker et al. (of record), Froehler et al. (of record), Taylor et al. (Drug Discov Today. 1999 Dec;4(12):562-567, newly cited), and Baracchini et al. (U.S. Patent Number 5,801,154, newly cited).

The invention of the above listed claims is drawn to an oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase of SEQ ID NO: 18, wherein said oligo is 10-40 nucleotides long, contains at least one phosphorothioate linkage, inhibits heparanase at least 50% as measured by western blot, wherein said oligo is made of DNA or RNA, or wherein said oligo is 15-25 nucleotides long, or is about 20 nucleotides long, or wherein said oligo comprises peptide-nucleic acid or morpholino linkages, or comprises internucleoside, sugar, or base modifications, or wherein said oligo is composed of 100% phosphorothioate linkages, or wherein the nucleobase is modified to comprise 5-methyl pyrimidine or 5-propynyl pyrimidine, or wherein said modified sugar moiety is a 2'-O-alkyl moiety, or wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase, and methods of use thereof.

Kussie et al. teach the sequence of a ribonucleic acid encoding a heparanase of SEQ ID NO: 18. Kussie et al. do not teach an antisense oligo that is 10-40 nucleotides long, contains at least one phosphorothioate linkage, inhibits heparanase at least 50% as measured by western blot, wherein said oligo is made of DNA or RNA, or wherein said oligo is 15-25 nucleotides long, or is about 20 nucleotides long, or wherein said oligo comprises peptide-nucleic acid or morpholino linkages, or comprises internucleoside, sugar, or base modifications, or wherein said oligo is composed of 100% phosphorothioate linkages, or wherein the nucleobase is modified to comprise 5-methyl pyrimidine or 5-propynyl pyrimidine, or wherein said modified sugar moiety is a 2'-O-alkyl moiety, or wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase, and methods of use thereof.

Pecker et al. teaches an antisense oligonucleotide to heparanase, albeit a different heparanase transcript than that which encodes the instantly contemplated SEQ ID NO:18, wherein said antisense molecule contains at least one phosphorothioate linkage, wherein said oligo is made of DNA or RNA, or wherein said oligo is more preferably 19-25 nucleotides long, which may comprise peptide-nucleic acid or morpholino linkages, and may comprise internucleoside, sugar, or base modifications, wherein said modified sugar moiety may be a 2'-O-alkyl moiety, or wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, or wherein the oligonucleotide inhibits expression of heparanase, and methods of use thereof.

Taylor et al. teaches that with available bioinformatics programs, one only needs to screen 3-6 oligomers per target in order to find one that can inhibit a gene with 66-95% efficiency.

Froehler et al. teaches 5-propynyl pyrimidine modifications of oligo nucleobases.

Baracchini et al. teach using inhibitory antisense oligos in combination with carriers capable of passing through the cell membrane, wherein said carrier is a membrane permeable cationic reagent, wherein said carrier is lipofectin.

It would have been obvious for one of ordinary skill in the art to use the heparanase sequence of Kussie et al., which encodes the amino acid sequence of SEQ ID NO:18, and make antisense oligos targeted to heparanase as taught by Pecker et al. Furthermore, it would have been obvious to incorporate 5-propynyl pyrimidine modifications into said antisense oligos as taught by Froehler et al., and to provide carriers for said compounds to traverse the cell membrane as taught by Baracchini et al.

One would have been motivated to make such antisense oligos, because Pecker et al. have already made such oligos targeting a closely related heparanase sequence, and because Pecker et al. further teach that chemical inhibitors of heparanase inhibited lung metastases induced by B16 melanoma, Lewis lung carcinoma and mammary adenocarcinoma cells. Thus, one of ordinary skill would have been motivated to find alternate inhibitors of heparanases so as to inhibit cancer, such as the instantly claimed antisense sequences targeting the heparanase of SEQ ID NO: 18. Furthermore one of ordinary skill in the would have been motivated to modify such sequences as taught by Froehler et al., because the oligos of Pecker et al. have already been

modified in order to confer nuclease resistance and enhance cellular entry, and because Froehler et al. teach that such 5-propynyl pyrimidine modifications, enhance binding of the antisense oligo to the target gene, and also enhance cellular entry, which are key steps in the mechanism of antisense oligo-mediated inhibition. Finally, one would have been motivated to combine the instantly contemplated oligos with carriers that enhance cellular entry as taught by Baracchini et al., because Pecker et al. taught carriers that confer enhanced cellular entry, and because Baracchini alos indicates that lipofectin enhances cellular entry.

One of ordinary skill in the art would have had a reasonable expectation of success of making such antisense oligos, because Pecker et al. already teach antisense oligos directed to a different heparanase transcript, and because Kussie et al. teach the instantly contemplated heparanase transcript of SEQ ID NO:18. One of ordinary skill could have easily made antisense oligos targeting Kussie's sequence since Pecker et al. teach such targeting to other heparanase sequences, and because Taylor et al. points out that with available bioinformatics programs, one only needs to screen 3-6 oligomers per target in order to find one that can inhibit a gene with 66-95% efficiency. One of ordinary skill would have had a reasonable expectation of success in incorporating the modifications of Froehler et al. into such antisense oligos, and also to combining antisense compounds with cationic carriers as taught by Baracchini et al., because both Froehler et al. and Baracchini et al. provide detailed instructions on their synthesis, and because such modifications and combinations are routinely performed by those of ordinary skill in the art.

Finally, Applicant has argued that the functional language in claim 1 whereby inhibition of the target is verified by western blot should be included as a claim limitation rather than being considered functional language which has no bearing on patentability. Further in response to this argument, Applicant is referred to the reference of Taylor et al. provided above, wherein it is stated that using available tools, it is within the capacity of one of ordinary skill in the art to synthesize antisense compounds with greater than 50% inhibitory capability with a reasonable amount of experimentation. The western blot limitation of the claims is considered to be no more than an intended use/functional limitation associated with what is actually a compound being claimed. It is not readily apparent from claim 1, the specification , applicant's arguments or otherwise, that such intended use recitation breathes any new significant or special property to what is otherwise a simple antisense oligonucleotide that would have been obvious in view of the collective art cited. Thus the western blot teaching of the claims is not considered to further distinguish what are considered to be obvious antisense compounds as claimed.

Note that claims 17-20 are included in this rejection under 35 U.S.C. § 103(a), even though the pharmaceutical language of said claims implies *in vivo* applicability and which intended use has been addressed under 35 U.S.C. § 112 1st paragraph enablement because for prior art purposes, intended use limitations for claimed compositions rarely breath life and meaning, and thus rarely provide patentable distinction, into what otherwise are known compositions. Such is the present case.

Allowable Subject Matter

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. A sequence search performed against the oligonucleotides of SEQ ID NOS: 3, 4, and 5 indicated no anticipating prior art. Thus the oligos of the independent SEQ ID NOS recited in claim 7 are considered free of the art if rewritten in independent form and including all of the limitations of claim 1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
March 9, 2003

JOHN L. LeGUYADER
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